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Qualitative Analysis of a Coupled Reaction–Diffusion Model in Biology with Time Delays

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Certain biochemical reaction can be modeled by a coupled system of time-delayed ordinary differential equations and linear parabolic partial differential equations. In a three-compartment model these equations are coupled through the boundary conditions. The aim of this paper is to give a qualitive analysis of this unusual coupled system. The analysis includes the existence and uniqueness of a global solution, explicit upper and lower bounds of the solution, and global stability of a steady-state solution. The global stability result is with respect to any nonnegative initial perturbation and is independent of the time delays in the process of reaction. Special attention is given to the Goodwin model for biochemical control of genes by a negative feedback mechanism with time delay and diffusion. © 1985 Academic Press, Inc.

I. INTRODUCTION

There have been numerous studies of mathematical models of biochemical systems in recent years. These models are formulated as a system of nonlinear differential equations and often contain either diffusion for spatial differences or time delays for certain biochemical processes. In this paper we study a model of three interacting compartments which includes a coupled system of differential equations with both time delay and diffusion. The model is motivated by Goodwin's model for biochemical control of genes by a negative feedback mechanism. Goodwin's model consists of a system of ordinary differential equations, however, he suggested that delays and spatial effects should be taken into account (cf. [3]). The first and third compartments are where the biochemical reactions occur. Each of these compartments is well mixed and has a differential delay equation governing the reactions of the chemical species. The second compartment, connecting the first and third, is nonreacting except for decay of

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the chemical species and accounts for spatial differences between the first and third compartments. The compartments are interconnected by permeable membranes which we assume to obey Fick's law of diffusion. With these assumptions the differential equations governing the chemical species, u_i, v_i in the ith compartment, $i=1, 2, 3$, are given by (cf. [4]).

$$\begin{aligned}
&u_1' + (a_1 + b_1)\, u_1 = a_1 u_2(0, t) + f(v_1(t - r_1)),\\
&v_1' + (a_1 + b_2)\, v_1 = a_1 v_2(0, t),\\
&(u_2)_t - D_1 (u_2)_{xx} + b_1 u_2 = 0,\\
&(v_2)_t - D_2 (v_2)_{xx} + b_2 v_2 = 0,\\
&u_3' + (a_3 + b_1)\, u_3 = a_3 u_2(l, t),\\
&v_3' + (a_3 + b_2)\, v_3 = a_3 v_2(l, t) + c_0 u_3(t - r_2) \quad (t > 0,\ 0 < x < l),
\end{aligned} \tag{1.1}$$

where $u_1' = du_1/dt$, $(u_2)_t = \partial u_2/\partial t$, etc. In the above equations, $a_i > 0$ are the membrane permeabilities, b_i and c_0 are positive constants corresponding to the reaction rates, $D_i > 0$ are diffusion coefficients, $r_i > 0$ are the time delays and f is a prescribed function representing the controlled production of u_1 by v_1. On the interface between compartments 1 and 2, and between compartments 2 and 3 the concentrations u_i, v_i are related by the boundary condition

$$\begin{aligned}
-(u_2)_x(0, t) + \beta_1 u_2(0, t) &= \beta_1 u_1(t)\\
(u_2)_x(l, t) + \beta_2 u_2(l, t) &= \beta_2 u_3(t)\\
-(v_2)_x(0, t) + \beta_1^* v_2(0, t) &= \beta_1^* v_1(t)\\
(v_2)_x(l, t) + \beta_2^* v_2(l, t) &= \beta_2^* v_3(t) \qquad (t > 0).
\end{aligned} \tag{1.2}$$

The initial condition for the system is given by

$$\begin{aligned}
&u_1(0) = \xi_1, && v_1(t) = \eta_1(t) && (-r_1 \leqslant t \leqslant 0),\\
&u_2(x, 0) = \xi_2(x), && v_2(x, 0) = \eta_2(x) && (0 < x < l),\\
&u_3(t) = \xi_3(t), && v_3(0) = \eta_3 && (-r_2 \leqslant t \leqslant 0).
\end{aligned} \tag{1.3}$$

In the boundary and initial conditions, $\beta_i > 0$, $\beta_i^* > 0$, $\xi_1 \geqslant 0$, $\eta_3 \geqslant 0$, $i = 1, 2$, are constants and ξ_2, ξ_3, η_1, η_2 are given continuous nonnegative functions of their respective arguments. The function $f(v)$ in Eq. (1.1) is assumed to be continuous nonnegative on $[0, \infty)$. Of special interest in our model is the function

$$f_0(v) = \sigma(1 + kv^\rho)^{-1}, \tag{1.4}$$

where σ and k are kinetic constants and $\rho \geqslant 1$ is the order of repression (cf. [4, 9]). A more detailed discussion of the three compartment model formulation given by Eqs. (1.1)–(1.3) can be found in [4]. A novelty of this system for the mathematical analysis is that the coupling of the various concentrations is through the boundary conditions.

The purpose of this paper is to give a qualitative analysis of the system (1.1)–(1.3). As little is known about coupled system of reaction–diffusion equations with time delays, especially about systems with coupled boundary conditions, our immediate concern is to establish the existence and uniqueness of a global classical solution. The existence–uniqueness proof is based on the monotone method for coupled reaction–diffusion systems through the boundary and the construction of the associated upper–lower solutions (cf. [5]). This method also leads to a comparison theorem and explicit upper and lower bounds of the solution. In fact, through suitable construction of some upper and lower solutions we show that problem (1.1)–(1.3) has a unique nonnegative solution which is uniformly bounded on $[0, l] \times [0, \infty)$. After establishing the existence uniqueness theorem our next concern is the stability problem of a steady-state solution. The existence and uniqueness of a positive steady-state solution for the case $f = f_0$ has been established in [4]. It is shown in this paper that for any function f satisfying

$$f(v) \geqslant 0, \qquad 0 \leqslant -f'(v) < b_1 b_2 / c_0 \quad \text{for } v \geqslant 0, \tag{1.5}$$

where $f'(v) \equiv df/dv$, the corresponding steady-state solution of (1.1)–(1.3) is globally asymptotically stable, independent of the time delays. Here the global asymptotic stability is with respect to nonnegative initial perturbations. This stability result is similar to the ones obtained by Allwright [1] and Banks and Mahaffy [2] for the Goodwin repression model with time delays only.

2. Monotone Sequences

In this section we describe an iterative scheme for the construction of a monotone nondecreasing sequence and a monotone nonincreasing sequence, both of which converge to a unique solution of the problem (1.1)–(1.3). The monotone behavior of these sequences is based on the property of upper and lower solutions which are taken as the initial iterations. The definition of upper–lower solutions depends on the monotone property of the reaction function (cf. [5]). Motivated by Goodwin's repression model where the reaction function f_0 has the form given by (1.4) we assume

$$\text{(H)} \quad f(v) \geqslant 0 \text{ and } f'(v) \leqslant 0 \quad \text{for } v \geqslant 0 \tag{2.1}$$

In (H) note that $f(v)$ is monotone nonincreasing in v.

Let $D_T=(0, T]\times(0, l)$, $\bar{D}_T=[0, T]\times[0, l]$ and let (u_i, v_i) represent the vector $(u_1, v_1, u_2, v_2, u_3, v_3)$, where $T>0$ can be arbitrarily large. Define the differential operators

$$\begin{aligned}
L_1[u_1] &\equiv u_1'+(a_1+b_1)\,u_1, & \mathscr{L}_1[v_1] &\equiv v_1'+(a_1+b_2)\,v_1,\\
L_2[u_2] &\equiv (u_2)_t-D_1(u_2)_{xx}+b_1u_2, & \mathscr{L}_2[v_2] &\equiv (v_2)_t-D_2(v_2)_{xx}+b_2v_2,\\
L_3[u_3] &\equiv u_3'+(a_3+b_1)\,u_3, & \mathscr{L}_3[v_3] &\equiv v_3'+(a_3+b_2)\,v_3,
\end{aligned}$$

and the boundary operators

$$\begin{aligned}
B[u_2](0) &\equiv -(u_2)_x(0, t)+\beta_1u_2(0, t),\\
B[u_2](l) &\equiv (u_2)_x(l, t)+\beta_2u_2(l, t),\\
\mathscr{B}[v_2](0) &\equiv -(v_2)_x(0, t)+\beta_1^*v_2(0, t),\\
\mathscr{B}[v_2](l) &\equiv (v_2)_x(l, t)+\beta_2^*v_2(l, t).
\end{aligned}$$

Then we can define the following upper–lower solutions.

DEFINITION 2.1. Two vector functions $(\tilde{u}_i, \tilde{v}_i)$ and $(\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ are called upper and lower solutions of (1.1)–(1.3), respectively, if they satisfy the differential inequalities

$$\begin{aligned}
&L_1[\tilde{u}_1]-a_1\tilde{u}_2(0, t)-f(\underset{\sim}{v}_1(t-r_1))\\
&\qquad\geqslant 0\geqslant L_1[\underset{\sim}{u}_1]-a_1\underset{\sim}{u}_2(0, t)-f(\tilde{v}_1(t-r_1)),\\
&\mathscr{L}_1[\tilde{v}_1]-a_1\tilde{v}_2(0, t)\geqslant 0\geqslant \mathscr{L}_1[\underset{\sim}{v}_1]-a_1\underset{\sim}{v}_2(0, t),\\
&L_2[\tilde{u}_2]\geqslant 0\geqslant L_2[\underset{\sim}{u}_2],\\
&\mathscr{L}_2[\tilde{v}_2]\geqslant 0\geqslant \mathscr{L}_2[\underset{\sim}{v}_2],\\
&L_3[\tilde{u}_3]-a_3\tilde{u}_2(l, t)\geqslant 0\geqslant L_3[\underset{\sim}{u}_3]-a_3\underset{\sim}{u}_2(l, t),\\
&\mathscr{L}_3[\tilde{v}_3]-a_3\tilde{v}_2(l, t)-c_0\tilde{u}_3(t-r_2)\\
&\qquad\geqslant 0\geqslant \mathscr{L}_3[\underset{\sim}{v}_3]-a_3\underset{\sim}{v}_2(l, t)-c_0\underset{\sim}{u}_3(t-r_2),\ (t, x)\in D_T,
\end{aligned}\tag{2.2}$$

the boundary inequalities

$$\begin{aligned}
&B[\tilde{u}_2](0)-\beta_1\tilde{u}_1(t)\geqslant 0\geqslant B[\underset{\sim}{u}_2](0)-\beta_1\underset{\sim}{u}_1(t),\\
&B[\tilde{u}_2](l)-\beta_2\tilde{u}_3(t)\geqslant 0\geqslant B[\underset{\sim}{u}_2](l)-\beta_2\underset{\sim}{u}_3(t),\\
&\mathscr{B}[\tilde{v}_2](0)-\beta_1^*\tilde{v}_1(t)\geqslant 0\geqslant \mathscr{B}[\underset{\sim}{v}_2](0)-\beta_1^*\underset{\sim}{v}_1(t),\\
&\mathscr{B}[\tilde{v}_2](l)-\beta_2^*\tilde{v}_3(t)\geqslant 0\geqslant \mathscr{B}[\underset{\sim}{v}_2](l)-\beta_2^*\underset{\sim}{v}_3(t) \qquad (t\in(0, T])
\end{aligned}\tag{2.3}$$

and the initial inequalities

$$\begin{aligned} &\tilde{u}_1(0) \geqslant \xi_1 \quad \geqslant \underset{\sim}{u}_1(0), && \tilde{v}_1(t) \geqslant \eta_1(t) \geqslant \underset{\sim}{v}_1(t) && (t \in [-r_1, 0]), \\ &\tilde{u}_2(x, 0) \geqslant \xi_2(x) \geqslant \underset{\sim}{u}_2(x, 0), && \tilde{v}_2(x, 0) \geqslant \eta_2(x) \geqslant \underset{\sim}{v}_2(x, 0) && (x \in (0, l)), \\ &\tilde{u}_3(t) \geqslant \xi_3(t) \geqslant \underset{\sim}{u}_3(t), && \tilde{v}_3(0) \geqslant \eta_3 \quad \geqslant \underset{\sim}{v}_3(0) && (t \in [-r_2, 0]). \end{aligned} \tag{2.4}$$

In the above definition the functions $(\tilde{u}_i, \tilde{v}_i)$ and $(\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ are required to be continuous in their respective domains and be once continuously differentiable in t and twice continuously differentiable in x for $(t, x) \in D_T$. In view of this definition every classical solution is an upper solution as well as a lower solution. As $f(v)$ is monotone nonincreasing in v the upper and lower solutions in (2.2) are related. The first inequality for an upper solution uses the function $\underset{\sim}{v}_1$, and the second inequality for a lower solution uses the function $\tilde{v}_1$.

Suppose upper and lower solutions $(\tilde{u}_i, \tilde{v}_i)$, $(\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ exist and $(\tilde{u}_i, \tilde{v}_i) \geqslant (\underset{\sim}{u}_i, \underset{\sim}{v}_i) \geqslant (0, 0)$. Then by starting from the initial iterations $(\bar{u}_i^{(0)}, \bar{v}_i^{(0)}) = (\tilde{u}_i, \tilde{v}_i)$ and $(\underset{\sim}{u}_i^{(0)}, \underset{\sim}{v}_i^{(0)}) = (\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ we can construct two sequences $\{\bar{u}_i^{(m)}, \bar{v}_i^{(m)}\}$, $\{\underset{\sim}{u}_i^{(m)}, \underset{\sim}{v}_i^{(m)}\}$ successively from the respective iteration processes:

$$\begin{aligned} &L_1[\bar{u}_1^{(m)}] = a_1 \bar{u}_2^{(m-1)}(0, t) + f(\underset{\sim}{v}_1^{(m-1)}(t - r_1)), \\ &\mathscr{L}_1[\bar{v}_1^{(m)}] = a_1 \bar{v}_2^{(m-1)}(0, t), \\ &L_2[\bar{u}_2^{(m)}] = 0, \\ &\mathscr{L}_2[\bar{v}_2^{(m)}] = 0, \\ &L_3[\bar{u}_3^{(m)}] = a_3 \bar{u}_2^{(m-1)}(l, t), \\ &\mathscr{L}_3[\bar{v}_3^{(m)}] = a_3 \bar{v}_2^{(m-1)}(l, t) + c_o \bar{u}_3^{(m-1)}(t - r_2) \end{aligned} \tag{2.5}$$

and

$$\begin{aligned} &L_1[\underset{\sim}{u}_1^{(m)}] = a_1 \underset{\sim}{u}_2^{(m-1)}(0, t) + f(\bar{v}_1^{(m-1)}(t - r_1)), \\ &\mathscr{L}_1[\underset{\sim}{v}_1^{(m)}] = a_1 \underset{\sim}{v}_2^{(m-1)}(0, t), \\ &L_2[\underset{\sim}{u}_2^{(m)}] = 0, \\ &\mathscr{L}_2[\underset{\sim}{v}^{(m)}] = 0, \\ &L_3[\underset{\sim}{u}_3^{(m)}] = a_3 \underset{\sim}{u}_2^{(m-1)}(l, t), \\ &\mathscr{L}_3[\underset{\sim}{v}_3^{(m)}] = a_3 \underset{\sim}{v}_2^{(m-1)}(l, t) + c_0 \underset{\sim}{u}_3^{(m-1)}(t - r_2). \end{aligned} \tag{2.6}$$

The boundary and initial conditions for both sequences are given in the form

$$\begin{aligned} B[u_2^{(m)}](0) &= \beta_1 u_1^{(m-1)}(t), \qquad & B[u_2^{(m)}](l) &= \beta_2 u_3^{(m-1)}(t), \\ \mathscr{B}[v_2^{(m)}](0) &= \beta_1^* v_1^{(m-1)}(t), \qquad & \mathscr{B}[v_2^{(m)}](l) &= \beta_2^* v_3^{(m-1)}(t), \end{aligned} \tag{2.7}$$

$$\begin{aligned} u_1^{(m)}(0) &= \xi_1, \qquad & v_1^{(m)}(t) &= \eta_1(t) \quad (t \in [-r_1, 0], \\ u_2^{(m)}(x, 0) &= \xi_2(x), \qquad & v_2^{(m)}(x, 0) &= \eta_2(x) \quad (x \in (0, l)), \\ u_3^{(m)}(t) &= \xi_3(t), \qquad & v_3^{(m)}(0) &= \eta_3 \quad (t \in [-r_2, 0]). \end{aligned} \tag{2.8}$$

It is clear that the sequences $\{\bar{u}_i^{(m)}, \bar{v}_i^{(m)}\}$, $\{\underline{u}_i^{(m)}, \underline{v}_i^{(m)}\}$ are well defined and can be determined by solving a linear scalar initial-value or initial boundary-value problem. To determine $(\bar{u}_i^{(m)}, \bar{v}_i^{(m)})$ or $(\underline{u}_i^{(m)}, \underline{v}_i^{(m)})$, it is necessary to calculate both $(\bar{u}_i^{(m-1)}, \bar{v}_i^{(m-1)})$ and $(\underline{u}_i^{(m-1)}, \underline{v}_i^{(m-1)})$ since the first equation in (2.5) uses $\underline{v}_1^{(m-1)}$ while the equation in (2.6) uses $\bar{v}_1^{(m-1)}$. Our main concern is to determine whether these two sequences converge and whether their limits are solutions of (1.1)–(1.3). In the remainder of this section we establish the convergence property of the sequences. This is contained in

LEMMA 2.1. *Let* $(\tilde{u}_i, \tilde{v}_i)$, $(\underline{u}_i, \underline{v}_i)$ *be upper and lower solutions with* $(\tilde{u}_i, \tilde{v}_i) \geqslant (\underline{u}_i, \underline{v}_i) \geqslant (0, 0)$ *and let hypothesis* (H) *hold. Then the sequence* $\{\bar{u}_i^{(m)}, \bar{v}_i^{(m)}\}$ *is monotone nonincreasing and* $\{\underline{u}_i^{(m)}, \underline{v}_i^{(m)}\}$ *is monotone nondecreasing. Moreover*

$$\begin{aligned} (\underline{u}_i^{(m-1)}, \underline{v}_i^{(m-1)}) &\leqslant (\underline{u}_i^{(m)}, \underline{v}_i^{(m)}) \leqslant (\bar{u}_i^{(m)}, \bar{v}_i^{(m)}) \\ &\leqslant (\bar{u}_i^{(m-1)}, \bar{v}_i^{(m-1)}), \qquad m = 1, 2, \ldots. \end{aligned} \tag{2.9}$$

Proof. Let $w_i = \bar{u}_i^{(0)} - \bar{u}_i^{(1)} = \tilde{u}_i - \bar{u}_i^{(1)}$, $z_i = \bar{v}_i^{(0)} - \bar{v}_i^{(1)} = \tilde{v}_i - \bar{v}_i^{(1)}$, $i = 1, 2, 3$. Then by (2.2), (2.4, (2.5), and (2.8), (w_1, z_1) satisfies the relation

$$\begin{aligned} L_1[w_1] &= L_1[\tilde{u}_1] - [a_1 \bar{u}_2^{(0)}(0, t) + f(\underline{v}_1^{(0)}(t - r_1))] \geqslant 0, \\ w_1(0) &= \tilde{u}_1(0) - \xi_1 \geqslant 0, \\ \mathscr{L}_1[z_1] &= \mathscr{L}_1[\tilde{v}_1] - a_1 \bar{v}_2^{(0)}(0, t) \geqslant 0, \\ z_1(t) &= \tilde{v}_1(t) - \eta_1(t) \geqslant 0 \qquad (t \in [-r_1, 0]). \end{aligned}$$

The above relation implies that $(w_1, z_1) \geqslant (0, 0)$ on $[0, T]$. Similarly, (w_3, z_3) satisfies

$$\begin{aligned} L_3[w_3] &= L_3[\tilde{u}_3] - a_3 \bar{u}_2^{(0)}(l, t) \geqslant 0, \\ w_3(t) &= \tilde{u}_3(t) - \xi_3(t) \geqslant 0 \qquad (t \in [-r_2, 0]), \\ \mathscr{L}_3[z_3] &= \mathscr{L}_3[\tilde{v}_3] - a_3 \bar{v}_2^{(0)}(l, t) - c_0 \bar{u}_3^{(0)}(t - r_2) \geqslant 0, \\ z_3(0) &= \tilde{v}_3(0) - \eta_3 \geqslant 0, \end{aligned}$$

which ensures that $(w_3, z_3) \geqslant (0, 0)$ on $[0, T]$. By the same reasoning, (w_2, z_2) satisfies

$$\begin{aligned}
&L_2[w_2] = L_2[\tilde{u}_2] - L_2[\bar{u}_2^{(1)}] = L_2[\tilde{u}_2] \geqslant 0,\\
&w_2(x, 0) = \tilde{u}_2(x, 0) - \xi_2(x) \geqslant 0,\\
&\mathscr{L}_2[z_2] = \mathscr{L}_2[\tilde{v}_2] - \mathscr{L}_2[\bar{v}_2^{(1)}] = \mathscr{L}_2[\tilde{v}_2] \geqslant 0,\\
&z_2(x, 0) = \tilde{v}_2(x, 0) - \eta_2(x) \geqslant 0.
\end{aligned}$$

From the boundary relations (2.3) and (2.7), we deduce

$$\begin{aligned}
&B[w_2](0) = B[\tilde{u}_2](0) - \beta_1 \bar{u}_1^{(0)}(t) \geqslant 0, \quad B[w_2](l) = B[\tilde{u}_2](l) - \beta_2 \bar{u}_3^{(0)}(t) \geqslant 0,\\
&\mathscr{B}[z_2](0) = \mathscr{B}[\tilde{v}_2](0) - \beta_1^* \bar{v}_1^{(0)}(t) \geqslant 0, \quad \mathscr{B}[z_2](l) = \mathscr{B}[\tilde{v}_2](l) - \beta_2^* \bar{v}_3^{(0)}(t) \geqslant 0.
\end{aligned}$$

It follows from these inequalities that $(w_2, z_2) \geqslant (0, 0)$ on $\bar{D}_T$ (cf. [6, 7]). This establishes the relation

$$(\bar{u}_i^{(1)}, \bar{v}_i^{(1)}) \leqslant (\bar{u}_i^{(0)}, \bar{v}_i^{(0)}) \qquad (i = 1, 2, 3).$$

A similar argument using relations (2.6)–(2.8) and the right-side inequalities in (2.2)–(2.4) shows that

$$(\underline{u}_i^{(0)}, \underline{v}_i^{(0)}) \leqslant (\underline{u}_i^{(1)}, \underline{v}_i^{(1)}) \qquad (i = 1, 2, 3).$$

Now let $w_i = \bar{u}_i^{(1)} - \underline{u}_i^{(1)}$, $z_i = \bar{v}_i^{(1)} - \underline{v}_i^{(1)}$. Then by (2.5), (2.6), and the non-increasing property of $f(v)$,

$$\begin{aligned}
&L_1[w_1] = a_1(\bar{u}_2^{(0)}(0, t) - \underline{u}_2^{(0)}(0, t)) + f(\underline{v}_1^{(0)}(t - r_1)) - f(\bar{v}_1^{(0)}(t - r_1)) \geqslant 0,\\
&\mathscr{L}_1[z_1] = a_1(\bar{v}_2^{(0)}(0, t) - \underline{v}_2^{(0)}(0, t)) \geqslant 0,\\
&L_2[w_2] = \mathscr{L}_2[z_2] = 0,\\
&L_3[w_3] = a_3(\bar{u}_2^{(0)}(l, t) - \underline{u}_2^{(0)}(l, t)) \geqslant 0,\\
&\mathscr{L}_3[z_3] = a_3(\bar{v}_2^{(0)}(l, t) - \underline{v}_2^{(0)}(l, t)) + c_0(\bar{u}_3^{(0)}(t - r_2) - \underline{u}_3^{(0)}(t - r_2)) \geqslant 0.
\end{aligned}$$

From the initial conditions, $w_i = z_i = 0$ at $t = 0$ ($z_1(t) = 0$ for $t \in [-r_1, 0]$ and $w_3(t) = 0$ for $t \in [-r_2, 0]$) and because (w_2, z_2) satisfies the boundary condition (2.7) we again conclude that $(w_i, z_i) \geqslant (0, 0)$ on $\bar{D}_T$. Hence

$$(\underline{u}_i^{(0)}, \underline{v}_i^{(0)}) \leqslant (\underline{u}_i^{(1)}, \underline{v}_i^{(1)}) \leqslant (\bar{u}_i^{(1)}, \bar{v}_i^{(1)}) \leqslant (\bar{u}_i^{(0)}, \bar{v}_i^{(0)}).$$

Assume for some $m > 1$,

$$(\underline{u}_i^{(m-1)}, \underline{v}_i^{(m-1)}) \leqslant (\underline{u}_i^{(m)}, \underline{v}_i^{(m)}) \leqslant (\bar{u}_i^{(m)}, \bar{v}_i^{(m)}) \leqslant (\bar{u}_i^{(m-1)}, \bar{v}_i^{(m-1)}).$$

Then by (2.5), (2.6), the functions $w_i = \underline{u}_i^{(m+1)} - \underline{u}_i^{(m)}$ and $z_i = \underline{v}_i^{(m+1)} - \underline{v}_i^{(m)}$ satisfy the respective relations

$$L_1[w_1] = a_1(\underline{u}_2^{(m)}(0,t) - \underline{u}_2^{(m-1)}(0,t)) + f(\bar{v}_1^{(m)}(t-r_1)) - f(\bar{v}^{(m-1)}(t-r_1)) \geqslant 0,$$

$$\mathscr{L}_1[z_1] = a_1(\underline{v}_2^{(m)}(0,t) - \underline{v}_2^{(m-1)}(0,t)) \geqslant 0,$$
$$L_2[w_2] = \mathscr{L}_2[z_2] = 0,$$
$$L_3[w_3] = a_3(\underline{u}_2^{(m)}(l,t) - \underline{u}_2^{(m-1)}(l,t)) \geqslant 0,$$
$$\mathscr{L}_3[z_3] = a_3(\underline{v}_2^{(m)}(l,t) - \underline{v}_2^{(m-1)}(l,t)) + c_0(\underline{u}_3^{(m)}(t-r_2) - \underline{u}_3^{(m-1)}(t-r_2)) \geqslant 0.$$

Since w_i and z_i also satisfy the same initial and boundary conditions as for the case $m=1$ we conclude that $(w_i, z_i) \geqslant (0,0)$. This proves the relation $(\underline{u}_i^{(m)}, \underline{v}_i^{(m)}) \leqslant (\underline{u}_i^{(m+1)}, \underline{v}_i^{(m+1)})$. The same argument gives the conclusion $(\bar{u}_i^{(m+1)}, \bar{v}_i^{(m+1)}) \leqslant (\bar{u}_i^{(m)}, \bar{v}_i^{(m)})$ and $(\underline{u}_i^{(m+1)}, \underline{v}_i^{(m+1)}) \leqslant (\bar{u}_i^{(m+1)}, \bar{v}_i^{(m+1)})$. The result of the lemma follows from the induction principle.

It is seen from Lemma 2.1 that the pointwise limits

$$\begin{aligned} \lim_{m\to\infty} (\bar{u}_i^{(m)}, \bar{v}_i^{(m)}) &= (\bar{u}_i, \bar{v}_i), \\ \lim_{m\to\infty} (\underline{u}_i^{(m)}, \underline{v}_i^{(m)}) &= (\underline{u}_i, \underline{v}_i), \end{aligned} \tag{2.10}$$

exist and satisfy the relation

$$(\underset{\sim}{u}_i, \underset{\sim}{v}_i) \leqslant (\underline{u}_i, \underline{v}_i) \leqslant (\bar{u}_i, \bar{v}_i) \leqslant (\tilde{u}_i, \tilde{v}_i). \tag{2.11}$$

Letting $m \to \infty$ in (2.5) and (2.6), a standard regularity argument shows that both $(\bar{u}_i, \bar{v}_i)$ and $(\underline{u}_i, \underline{v}_i)$ satisfy Eqs. (1.1)–(1.3) except with the first equation in (1.1) replaced, respectively, by

$$\begin{aligned} L_1[\bar{u}_1] &= a_1 \bar{u}_2(0,t) + f(\underline{v}_1(t-r_1)), \\ L_1[\underline{u}_1] &= a_1 \underline{u}_2(0,t) + f(\bar{v}_1(t-r_1)) \end{aligned} \tag{2.12}$$

(cf. [5]). Hence $(\bar{u}_i, \bar{v}_i)$ and $(\underline{u}_i, \underline{v}_i)$ are not necessarily solutions of (1.1)–(1.3) unless $\bar{v}_1(t) = \underline{v}_1(t)$ for every $t \geqslant 0$. In the next section we show that $\bar{v}_1 = \underline{v}_1$ and $(\bar{u}_i, \bar{v}_i)$ is the unique solution of (1.1)–(1.3).

3. Existence and Boundedness of a Solution

To ensure the existence of a global solution to the system (1.1)–(1.3) we need to show that upper and lower solutions do exist and the limits $(\bar{u}_i, \bar{v}_i)$

and $(\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ in (2.10) coincide. We first establish an existence theorem whenever upper–lower solutions exist.

THEOREM 3.1. *Let $(\tilde{u}_i, \tilde{v}_i)$, $(\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ be upper and lower solutions with $(\tilde{u}_i, \tilde{v}_i) \geqslant (\underset{\sim}{u}_i, \underset{\sim}{v}_i) \geqslant (0, 0)$ and let f satisfy hypothesis* (H). *Then the sequences $\{\bar{u}_i^{(m)}, \bar{v}_i^{(m)}\}$, $\{\underset{\sim}{u}_i^{(m)}, \underset{\sim}{v}_i^{(m)}\}$ obtained from* (2.5)–(2.8) *with $(\bar{u}_i^{(0)}, \bar{v}_i^{(0)}) = (\tilde{u}_i, \tilde{v}_i)$ and $(\underset{\sim}{u}_i^{(0)}, \underset{\sim}{v}_i^{(0)}) = (\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ converge monotonically from above and below, respectively, to a unique solution (u_i, v_i) such that*

$$(\underset{\sim}{u}_i, \underset{\sim}{v}_i) \leqslant (u_i, v_i) \leqslant (\tilde{u}_i, \tilde{v}_i) \qquad ((t, x) \in \bar{D}_T). \tag{3.1}$$

Proof. Since $\bar{u}_3(t) = \underset{\sim}{u}_3(t) = \xi_3(t)$ for $t \in [-r_2, 0]$ and $\bar{v}_1(t) = \underset{\sim}{v}_1(t) = \eta_1(t)$ for $t \in [-r_1, 0]$ it suffices to show that $(\bar{u}_i, \bar{v}_i) = (\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ for $(t, x) \in \bar{D}_T$. To achieve this we let $w_i = \bar{u}_i - \underset{\sim}{u}_i$, $z_i = \bar{v}_i - \underset{\sim}{v}_i$, $i = 1, 2, 3$. Then

$$\begin{aligned}
&L_1[w_1] = a_1 w_2(0, t) + f(\underset{\sim}{v}_1(t - r_1)) - f(\bar{v}_1(t - r_1)),\\
&\mathscr{L}_1[z_1] = a_1 z_2(0, t),\\
&L_2[w_2] = 0, \qquad B[w_2](0) = \beta_1 w_1(t), \qquad B[w_2](l) = \beta_2 w_3(t),\\
&\mathscr{L}_2[z_2] = 0, \qquad \mathscr{B}[z_2](0) = \beta_1^* z_1(t), \qquad \mathscr{B}[z_2](l) = \beta_2^* z_3(t),\\
&L_3(w_3] = a_3 w_2(l, t),\\
&\mathscr{L}_3[z_3] = a_3 z_2(l, t) + c_0 w_3(t - r_2),\\
&\quad w_1(0) = w_2(x, 0) = w_3(0) = 0, \qquad z_1(0) = z_2(x, 0) = z_3(0) = 0.
\end{aligned} \tag{3.2}$$

In terms of integral representation, (w_i, z_i) for $i = 1$, and $i = 3$ are given by

$$\begin{aligned}
&w_1(t) = \int_0^t e^{-\alpha_1(t-\tau)}[a_1 w_2(0, \tau) + f(\underset{\sim}{v}_1(\tau - r_1)) - f(\bar{v}_1(\tau - r_1))]\, d\tau,\\
&z_1(t) = a_1 \int_0^t e^{-\alpha_2(t-\tau)} z_2(0, \tau)\, d\tau,\\
&w_3(t) = a_3 \int_0^t e^{-\alpha_3(t-\tau)} w_2(l, \tau)\, d\tau,\\
&z_3(t) = \int_0^t e^{-\alpha_4(t-\tau)}[a_3 z_2(l, \tau) + c_0 w_3(\tau - r_2)]\, d\tau,
\end{aligned} \tag{3.3}$$

where $\alpha_1 = a_1 + b_1$, $\alpha_2 = a_1 + b_2$, $\alpha_3 = a_3 + b_1$, $\alpha_4 = a_3 + b_2$. Let

$$M^* = \max\{f'(v); \underset{\sim}{v}_1 \leqslant v \leqslant \tilde{v}_1, t \in [0, T]\}, \tag{3.4}$$

and for each fixed $t \geqslant 0$ let $\|w\|_t$ be the maximum norm of either $w(\tau)$ on

$[0, t]$ or $w(\tau, x)$ on $[0, t] \times [0, l]$. In view of $\underline{v}_1(\tau - r_1) = \bar{v}_1(\tau - r_1)$ for $\tau \in [0, r_1]$ and $w_3(\tau - r_2) = 0$ for $\tau \in [0, r_2]$ we obtain from (3.3)

$$\begin{aligned} |w_1(t)| &\leqslant \alpha_1^{-1}(1 - e^{-\alpha_1 t})(a_1 \|w_2\|_t + M^* \|z_1\|_t) \\ &\leqslant M(1 - e^{-\alpha_1 t})(\|w_2\|_t + \|z_1\|_t), \\ |z_1(t)) &\leqslant M(1 - e^{-\alpha_2 t}) \|z_2\|_t, \\ |w_3(t)| &\leqslant M(1 - e^{-\alpha_3 t}) \|w_2\|_t, \\ |z_3(t)| &\leqslant M(1 - e^{-\alpha_4 t})(\|z_2\|_t + \|w_3\|_t), \end{aligned} \tag{3.5}$$

where M is a positive constant independent of t.

To obtain an estimate for (w_2, z_2) we also use an integral representation in terms of the Green's function $G(x, t \mid \xi, \tau)$. For each fixed $(\xi, \tau) \in D_T$ this function is governed by the equations

$$\begin{aligned} \hat{L}[G] &\equiv G_t - DG_{xx} + bG = \delta(x - \xi)\, \delta(t - \tau) \\ \hat{B}[G](0) &\equiv -G_x(0, t \mid \xi, \tau) + \hat{\beta}_1 G(0, t \mid \xi, \tau) = 0, \\ \hat{B}[G](l) &\equiv G_x(l, t \mid \xi, \tau) + \hat{\beta}_2 G(l, t \mid \xi, \tau) = 0, \\ G(x, t \mid \xi, \tau) &\equiv 0 \qquad (t < \tau), \end{aligned} \tag{3.6}$$

where D, b, $\hat{\beta}_1$, $\hat{\beta}_2$ are positive constants. Denote by G_1, G_2 the Green's function corresponding to $\hat{L} = L_2$, $\hat{B} = B$, and $\hat{L} = \mathscr{L}_2$, $\hat{B} = \mathscr{B}$, respectively. Then the integral representation for the solutions w_2, z_2 in (3.2) are given by

$$\begin{aligned} w_2(x, t) &= \int_0^t [\beta_1 G_1(x, t \mid 0, \tau)\, w_1(\tau) + \beta_2 G_1(x, t \mid l, \tau)\, w_3(\tau)]\, d\tau, \\ z_2(x, t) &= \int_0^t [\beta_1^* G_2(x, t \mid 0, \tau)\, z_1(\tau) + \beta_2^* G_2(x, t \mid l, \tau)\, z_3(\tau)]\, d\tau \end{aligned} \tag{3.7}$$

(e.g. see [8, p. 199]). To determine the Green's function we write

$$G(x, t \mid \xi, \tau) = \Gamma(x, t \mid \xi, \tau) + V(x, t \mid \xi, \tau),$$

where Γ is the fundamental solution of the operator $\hat{L}$ in $\mathbb{R}^1$ and V is determined from the usual initial boundary value problem

$$\begin{aligned} \hat{L}[V] &= 0, \\ \hat{B}[V](0) &= -\hat{B}[\Gamma](0), \\ \hat{B}[V](l) &= -\hat{B}[\Gamma](l), \\ V(x, t \mid \xi, \tau) &\equiv 0 \text{ for } t < \tau \qquad (x, t) \in D_T. \end{aligned} \tag{3.8}$$

The fundamental solution Γ is given explicitly by

$$\Gamma(x, t \mid \xi, \tau) = H(t-\tau)(4\pi(t-\tau)/D)^{-1/2}\exp[-(b + D|x-\xi|^2/4|t-\tau|)], \tag{3.9}$$

where $H(t)$ is the Heaviside function. Clearly $G = \Gamma + V$ satisfies all the requirements in (3.6). Although Γ has a weak singular point at (ξ, τ) the function V is a bounded smooth function in D_T for any fixed (ξ, τ). In view of (3.8), (3.9),

$$|G(x, t \mid \xi, \tau)| \leqslant (4\pi(t-\tau)/D)^{-1/2} + M_0 \qquad (t > \tau), \tag{3.10}$$

where M_0 is an upper bound of V on $\bar{D}_T$. By applying the above estimate in (3.7) for G_1 and G_2 we have

$$\begin{aligned} |w_2(x, t)| &\leqslant M_1\left(\int_0^t ((t-\tau)^{-1/2} + M_0)\, d\tau\right)(\|w_1\|_t + \|w_3\|_t) \\ &\leqslant c_1(t^{1/2} + t)(\|w_1\|_t + \|w_3\|_t), \\ |z_2(x, t)| &\leqslant c_1(t^{1/2} + t)(\|z_1\|_t + \|z_3\|_t), \end{aligned} \tag{3.11}$$

where c_1 is a positive constant independent of (t, x).

Let $W = (w_i, z_i)$ and for each $t > 0$ define

$$\begin{aligned} |W(x, t)| &= |w_1(t)| + |z_1(t)| + |w_2(x, t)| + \cdots + |z_3(t)|, \\ \|W\|_t &= \|w_1\|_t + \|z_1\|_t + \|w_2\|_t + \cdots + \|z_3\|_t. \end{aligned} \tag{3.12}$$

Then by adding the inequalities in (3.5) and (3.11) we obtain

$$|W(x, t)| \leqslant c(1 - e^{-\alpha_0 t} + t^{1/2} + t)\, \|W\|_t \quad ((x, t) \in D_T)$$

for some positive constants c and α_0. Let t_1 be any constant such that $c(1 - e^{-\alpha_0 t_1} + t_1^{1/2} + t_1) < 1$. Since $\|W\|_t$ is a nondecreasing function of t the above relation implies that

$$\|W\|_t \leqslant (1 - e^{-\alpha_0 t_1} + t_1^{1/2} + t_1)\, \|W\|_{t_1} \quad \text{for all } t \in [0, t_1].$$

By the choice of t_1 this relation can hold only when $\|W\|_{t_1} = 0$. This leads to the conclusion $(\bar{u}_i, \bar{v}_i) = (\underline{u}_i, \underline{v}_i)$ on $[0, l] \times [0, t_1]$. Since the constants c and α_0 are independent of t a continuation of the above argument shows that $(\bar{u}_i, \bar{v}_i) = (\underline{u}_i, \underline{v}_i)$ on $\bar{D}_T$. It also shows that $(\bar{u}_i, \bar{v}_i)$ is the unique solution of (1.1)–(1.3). Finally, the monotone convergence of the sequences and the relation (3.1) follow from Lemma 2.1. This completes the proof of the theorem.

It is seen from Theorem 3.1 that the existence of a solution to (1.1)–(1.3) is ensured if there is a suitable pair of upper and lower solutions. Since every solution is an upper solution as well as a lower solution, the existence of such a pair becomes both necessary and sufficient for the existence problem. To construct some explicit upper–lower solutions so that a global solution is guaranteed to exist we choose the constant functions $(\tilde{u}_i, \tilde{v}_i) = (\rho_i, \rho_i^*)$ and $(\underset{\sim}{u}_i, \underset{\sim}{v}_i) = (0, 0)$, where ρ_i, ρ_i^* are some positive constants satisfying

$$\rho_i \geqslant \bar{\xi}_i, \qquad \rho_i^* \geqslant \bar{\eta}_i, \quad i = 1, 2, 3. \tag{3.13}$$

The constants $\bar{\xi}_i$, $\bar{\eta}_i$ are the least upper bounds of the initial functions ξ_i, η_i in their respective domain. In view of Definition 2.1, the pair (ρ_i, ρ_i^*) and $(0, 0)$ fulfills the requirements in (2.2) if

$$\begin{gathered}
(a_1 + b_1)\, \rho_1 - a_1 \rho_2 - f(0) \geqslant 0 \geqslant -f(\rho_1^*),\\
(a_1 + b_2)\, \rho_1^* - a_1 \rho_2^* \geqslant 0,\\
(a_3 + b_1)\, \rho_3 - a_3 \rho_2 \geqslant 0,\\
(a_3 + b_2)\, \rho_3^* - a_3 \rho_2^* - c_0 \rho_3 \geqslant 0;
\end{gathered}$$

choose

$$\rho_2 = (1 + b_1/a_3)\, \rho_3, \qquad \rho_2^* = (1 + b_2/a_1)\, \rho_1^*. \tag{3.14}$$

Then from $f(\rho_1^*) \geqslant 0$ the above inequalities hold when

$$\begin{aligned}
(1 + b_1/a_1)\, \rho_1 &\geqslant (1 + b_1/a_3)\, \rho_3 + f(0)/a_1,\\
(1 + b_2/a_3)\, \rho_3^* &\geqslant (1 + b_2/a_1)\, \rho_1^* + (c_0/a_3)\, \rho_3.
\end{aligned} \tag{3.15}$$

To fulfill the boundary requirements in (2.3), (ρ_i, ρ_i^*) must also satisfy the relation

$$\begin{aligned}
\beta_1 \rho_2 - \beta_1 \rho_1 &\geqslant 0, & \beta_2 \rho_2 - \beta_2 \rho_3 &\geqslant 0,\\
\beta_1^* \rho_2^* - \beta_1^* \rho_1^* &\geqslant 0, & \beta_2^* \rho_2^* - \beta_2^* \rho_3^* &\geqslant 0.
\end{aligned}$$

By the choice of ρ_2, ρ_2^* in (3.14) it suffices to verify

$$(1 + b_1/a_3)\, \rho_3 \geqslant \rho_1, \qquad (1 + b_2/a_1)\, \rho_1^* \geqslant \rho_3^*. \tag{3.16}$$

This relation together with (3.15) can be put in the form

$$\begin{aligned}
&1 + b_1/a_3 \geqslant \rho_1/\rho_3 \geqslant (1 + b_1/a_3)/(1 + b_1/a_1) + (f(0)/(a_1 + b_1)\, \rho_3),\\
&1 + b_2/a_1 \geqslant \rho_3^*/\rho_1^* \geqslant (1 + b_2/a_1)/(1 + b_2/a_3) + (c_0/(a_3 + b_2))(\rho_3/\rho_1^*).
\end{aligned} \tag{3.17}$$

Let ρ_3 be any large constant such that

$$f(0)/((a_1+b_1)\,\rho_3) \leqslant (1+b_1/a_3)(b_1/(a_1+b_1)).$$

Then there exists $\rho_1 > 0$ such that (ρ_1/ρ_3) satisfies the relation in (3.17). By taking ρ_3 sufficiently large, if necessary, the constants ρ_i, $i=1, 2, 3$, can be chosen to satisfy the initial inequalities in (3.13). With ρ_3 fixed we then choose ρ_1^* sufficiently large such that

$$1+b_2/a_1 \geqslant (1+b_2/a_1)/(1+b_2/a_3) + (c_0/(a_3+b_2))(\rho_3/\rho_1^*).$$

The above relation ensures that for some $\rho_3^* > 0$ the second relation in (3.17) holds. With this choice of ρ_i, ρ_i^* for $i=1,3$ and the relation (3.14) for $i=2$ the functions (ρ_i, ρ_i^*) and $(0, 0)$ satisfy all the requirements in (2.2)–(2.4). In view of Theorem 3.1 we have the following global existence theorem.

THEOREM 3.2. *Let f satisfy hypothesis* (H). *Then there exist positive constants ρ_i, ρ_i^* such that a unique global solution (u_i, v_i) to the problem* (1.1)–(1.3) *exists and satisfies the relation*

$$(0,0) \leqslant (u_i, v_i) \leqslant (\rho_i, \rho_i^*) \qquad (t>0,\ x \in [0, l]). \tag{3.18}$$

Moreover, the bound (ρ_i, ρ_i^*) can be determined from (3.14) *and* (3.17).

Since the function $f_0(v)$ satisfies hypothesis (H) we immediately have the following result.

COROLLARY. *The problem* (1.1)–(1.3) *with $f=f_0$ given by* (1.4) *has a unique bounded nonnegative solution (u_i, v_i) which satisfies the relation* (3.18).

4. GLOBAL ASYMPTOTIC STABILITY

The existence–comparison theorem for the time-dependent problem (1.1)–(1.3) can be used to investigate the stability property of a steady-state solution. In this section we give a sufficient condition for the global asymptotic stability of a steady-state solution. This global stability result is with respect to any nonnegative initial function and is independent of the time delays r_1, r_2. The existence and uniqueness problem of the steady-state has been discussed in [4].

THEOREM 4.1. *Let (u_i^s, v_i^s) be a nonnegative steady-state solution of* (1.1), (1.2), *and let f satisfy hypothesis* (H). *If, in addition,*

$$\sup_{v_1 \geqslant 0} [-f'(v_1)] < b_1 b_2 / c_0, \tag{4.1}$$

then for any nonnegative initial function (ξ_i, η_i), there exist positive constants M, ε, independent of the time delays r_1, r_2, such that the corresponding time-dependent solution (u_i, v_i) satisfies the relation

$$\begin{aligned} &|u_i(t) - u_i^s| \leqslant Me^{-\varepsilon t}, \ |v_i(t) - v_i^s| \leqslant Me^{-\varepsilon t}, && i = 1, 3, \\ &|u_2(t, x) - u_2^s(x)| \leqslant Me^{-\varepsilon t}, \ |v_2(t, x) - v_2^s(x)| \leqslant Me^{-\varepsilon t} && (t > 0, 0 \leqslant x \leqslant l). \end{aligned} \tag{4.2}$$

Proof. We apply Theorem 3.1 by constructing a suitable pair of upper and lower solutions in the form

$$(\tilde{u}_i, \tilde{v}_i) = (u_i^s + p(t), v_i^s + q(t)),$$

$$(\underset{\sim}{u}_i, \underset{\sim}{v}_i) = (u_i^s - p^*(t), v_i^{(s)} - q^*(t)),$$

where p, q, p^*, and q^* are nonnegative functions to be determined. It is clear by taking $p(0)$, $q(0)$, $p^*(0)$, $q^*(0)$, sufficiently large, if necessary, the initial requirements in (2.4) are satisfied. The boundary inequalities (2.3) are also satisfied if

$$B[u_2^s](0) + \beta_1 p - \beta_1(u_1^s + p) \geqslant 0 \geqslant B[u_2^s](0) - \beta_1 p^* - \beta_1(u_1^s - p^*),$$

$$B[u_2^s](l) + \beta_2 p - \beta_2(u_3^s + p) \geqslant 0 \geqslant B[u_2^s](l) - \beta_2 p^* - \beta_2(u_3^s - p^*),$$

$$\mathscr{B}[v_2^s](0) + \beta_1^* q - \beta_1^*(v_1^s + q) \geqslant 0 \geqslant \mathscr{B}[v_2^s](0) - \beta_1^* q^* - \beta_1^*(v_1^s - q^*),$$

$$\mathscr{B}[v_2^s](l) + \beta_2^* q - \beta_2^*(v_3^s + q) \geqslant 0 \geqslant \mathscr{B}[v_2^s](l) - \beta_2^* q^* - \beta_2^*(v_3^s - q^*).$$

Since (u_i^s, v_i^s) satisfies boundary condition (1.2) all the above inequalities hold for any functions p, q, p^*, q^*. Hence it suffices to find suitable functions p, q, p^*, and q^* such that the differential inequalities (2.2) are satisfied.

Now $(\tilde{u}_i, \tilde{v}_i)$ fulfills the left-side differential inequalities in (2.2) if

$$p' + (a_1 + b_1)(u_1^s + p) - a_1(u_2^s(0) + p) - f(\underset{\sim}{v}_1(t - r_1)) \geqslant 0,$$

$$q' + (a_1 + b_2)(v_1^s + q) - a_1(v_2^s(0) + q) \geqslant 0,$$

$$p' - D_1(u_2^s)_{xx} + b_1(u_2^s + p) \geqslant 0,$$

$$q' - D_2(v_2^s)_{xx} + b_2(v_2^s + q) \geqslant 0,$$

$$p' + (a_3 + b_1)(u_3^s + p) - a_3(u_2^s(l) + p) \geqslant 0,$$

$$q' + (a_3 + b_2)(v_3^s + q) - a_3(v_2^s(l) + q) - c_0(u_3^s + p(t - r_2)) \geqslant 0,$$

where $\underset{\sim}{v}_1(t-r_1)=v_1^s-q^*(t-r_1)$. Since (u_i^s, v_i^s) satisfies Eq. (1.1) these inequalities are equivalent to

$$\begin{aligned}
p'+(a_1+b_1)\,p-a_1p &\geqslant f(\underset{\sim}{v}_1(t-r_1))-f(v_1^s),\\
q'+(a_1+b_2)\,q-a_1q &\geqslant 0,\\
p'+b_1p &\geqslant 0,\\
q'+b_2q &\geqslant 0,\\
p'+(a_3+b_1)\,p-a_3p &\geqslant 0,\\
q'+(a_3+b_2)\,q-a_3q &\geqslant c_0p(t-r_2).
\end{aligned}$$

In view of the relation

$$|f(\underset{\sim}{v}_1(t-r_1))-f(v_1^s)|\leqslant M^*(v_1^s-\underset{\sim}{v}_1(t-r_1))=M^*q^*(t-r_1)$$

all the above inequalities hold whenever

$$\begin{aligned}
p'+b_1p &\geqslant M^*q^*(t-r_1),\\
q'+b_2q &\geqslant c_0p(t-r_2) \qquad (t>0).
\end{aligned} \tag{4.3}$$

Following the same reasoning as for $(\tilde{u}_i, \tilde{v}_i)$, the function $(\underset{\sim}{u}_i, \underset{\sim}{v}_i)=(u_i^s-p^*, v_i^s-q^*)$ fulfills the right-side differential inequalities in (2.2) if (p^*, q^*) satisfies the relation

$$\begin{aligned}
(p^*)'+b_1\,p^* &\geqslant M^*q(t-r_1),\\
(q^*)'+b_2q^* &\geqslant c_0p^*(t-r_2) \qquad (t>0).
\end{aligned} \tag{4.4}$$

Choose

$$p=p_0e^{-\varepsilon t}, \quad q=q_0e^{-\varepsilon t}, \quad p^*=p_0^*e^{-\varepsilon t}, \quad q^*=q_0e^{-\varepsilon t},$$

where $\varepsilon>0$ is a constant to be determined. Then relations (4.3), (4.4) become

$$\begin{aligned}
(b_1-\varepsilon)\,p_0 &\geqslant M^*q_0^*e^{\varepsilon r_1}, &\qquad (b_2-\varepsilon)\,q_0 &\geqslant c_0p_0e^{\varepsilon r_2},\\
(b_1-\varepsilon)\,p_0^* &\geqslant M^*q_0e^{\varepsilon r_1}, &\qquad (b_2-\varepsilon)\,q_0^* &\geqslant c_0p_0^*e^{\varepsilon r_2}.
\end{aligned}$$

By taking $q_0=q_0^*$, $p_0=p_0^*$ it suffices to find p_0, q_0 such that

$$M^*e^{\varepsilon r_1}/(b_1-\varepsilon)\leqslant p_0/q_0\leqslant(b_2-\varepsilon)/c_0e^{\varepsilon r_2}.$$

The existence of such a pair of (p_0, q_0) is possible whenever

$$M^*c_0\leqslant(b_1-\varepsilon)(b_2-\varepsilon)\,e^{-\varepsilon(r_1+r_2)}.$$

In view of (4.1) the above relation is clearly satisfied by a sufficiently small $\varepsilon > 0$. With this choice of ε and suitably large p_0, q_0 (see Remark 4.1), the functions $(u_i^s + p,\ v_i^s + q)$ and $(u_i^s - p^*,\ v_i^s - q^*)$ are upper and lower solutions. The result (5.2) follows from Theorem 3.1.

Remark 4.1. When $p^*(0)$, $q^*(0)$ are large the lower solution $(\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ may become negative and Theorem 3.1 is not directly applicable. To overcome this we define a modified function $\hat{f}$ of f so that $\hat{f}(v) = f(v)$ for $v \geq 0$ and $\hat{f}$ is nonnegative and nonincreasing for $v < 0$ (e.g., $\hat{f}(v) = f(0)$ for all $v < 0$). It is easily seen from the proof of Theorem 3.1 that if the lower solution $(\underset{\sim}{u}_i, \underset{\sim}{v}_i)$ is not nonnegative all the conclusions in the theorem remain true when $\hat{f}$ is replaced by f. Clearly $(u_i^s - p^*,\ v_i^s - q^*)$ is a lower solution of the modified problem (i.e., with f replaced by $\hat{f}$). Since by Theorem 3.2 the solution of (1.1)–(1.3) is unique and nonnegative whenever the initial function is nonnegative we conclude that the solution of the modified problem must coincide with the solution of the original problem. This implies that the result in (4.2) remains true even if $(u_i^s - p^*,\ v_i^s - q^*)$ assumes negative values in its domain.

It is seen from Theorem 4.1 that if f satisfies (H) and (4.1) the steady-state solution of (1.1), (1.2) is globally asymptotically stable. In the special case of $f = f_0$ the maximum of $(-f'(v))$ occurs at $\hat{v} \equiv ((\rho - 1)/k(\rho + 1))^{1/\rho}$ and

$$-f'(\hat{v}) = \begin{cases} \sigma k & \text{for } \rho = 1 \\ \sigma k^{1/\rho}(4\rho)^{-1}(\rho - 1)^{1 - 1/\rho}(\rho + 1)^{1 + 1/\rho} & \text{for } \rho > 1. \end{cases} \tag{4.5}$$

In view of Theorem 4.1 we have

COROLLARY. *Let (u_i^s, v_i^s) be the nonnegative steady-state solution of* (1.1), (1.2) *corresponding to $f = f_0$, where f_0 is given by* (1.4). *If*

$$\begin{aligned} &\sigma k < b_1 b_2 / c_0 && \text{when } \rho = 1, \\ &\sigma k^{1/\rho} \rho^{-1} (\rho - 1)^{1 - 1/\rho} (\rho + 1)^{1 + 1/\rho} < 4 b_1 b_2 / c_0 && \text{when } \rho > 1, \end{aligned} \tag{4.6}$$

then (u_i^s, v_i^s) is globally asymptotically stable with respect to nonnegative initial functions.

REFERENCES

1. D. J. ALLWRIGHT, A global stability criterion for simple control loops, *J. Math. Biol.* **4** (1977), 363–373.
2. H. T. BANKS AND J. M. MAHAFFY, Global asymptotic stability of certain models for protein synthesis and repression, *Quart. Appl. Math.* **36** (1978), 209–221.

3. B. C. GOODWIN, Oscillatory behavior in enzymatic control processes, *Adv. Enzyme Reg.* **3** (1965), 425–439.
4. J. M. MAHAFFY AND C. V. PAO, Models of genetic control by repression with time delays and spatial effects, *J. Math. Biology* **20** (1984), 39–57.
5. C. V. PAO, Reaction diffusion equations with nonlinear boundary conditions, *J. Nonlinear Anal. TMA* **5** (1981), 1077–1094.
6. C. V. PAO, Positive solution of a nonlinear boundary value problem of parabolic type, *J. Differential Equations* **22** (1976), 452–461.
7. M. H. PROTTER AND H. F. WEINBERGER, "Maximum Principles in Differential Equations," Prentice-Hall, Englewood Cliffs, New Jersey, 1967.
8. I. STAKGOLD, "Boundary Value Problems of Mathematical Physics," Vol. II, MacMillion Co., New York, 1968.
9. J. J. TYSON AND H. G. OTHMER, The dynamics of feedback control circuits in biochemical pathways, *in* "Prog. in Theor. Biol." (R. Rosen and F. M. Snell, Eds.), Academic Press, New York, 1978.